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Abstract: Immunotherapy leads to significantly prolonged survival of patients with metastatic melanoma. Autoimmune side effects including colitis, dermatitis, and endocrine abnormalities are common in patients treated with ipilimumab [anti-CTLA4 (cytotoxic T-lymphocyte-associated protein 4)]. Antibodies such as pembrolizumab that interfere with the PD-1 (programmed cell death 1)/PD-L1 pathway show greater efficacy and less toxicity than ipilimumab. Here we report 2 cases of pembrolizumab-induced uveitis associated with complete or partial tumor response. We suggest that uveitis may serve as a surrogate marker for a tumor response to therapy with pembrolizumab.

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Pembrolizumab-triggered Uveitis: An Additional Surrogate Marker for Responders in Melanoma Immunotherapy?

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Summary: Immunotherapy leads to significantly prolonged survival of patients with metastatic melanoma. Autoimmune side effects including colitis, dermatitis, and endocrine abnormalities are common in patients treated with ipilimumab [anti-CTLA4 (cytotoxic T-lymphocyte-associated protein 4)]. Antibodies such as pembrolizumab that interfere with the PD-1 (programmed cell death 1)/PD-L1 pathway show greater efficacy and less toxicity than ipilimumab. Here we report 2 cases of pembrolizumab-induced uveitis associated with complete or partial tumor response. We suggest that uveitis may serve as a surrogate marker for a tumor response to therapy with pembrolizumab.

Key Words: melanoma, immunotherapy, uveitis

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BACKGROUND

Immunotherapy has dramatically improved the prognosis of metastatic melanoma. Although ipilimumab, the first-in-class antibody targeting a lymphocyte inhibitory receptor (checkpoint), showed a response rate of around 10%–15%, it can lead to life-threatening autoimmune adverse events.[1,2] Programmed cell death 1 (PD-1)-specific antibodies, including pembrolizumab, demonstrate greater efficacy and less toxicity than compared with ipilimumab.[3–5] According to common toxicity criteria version 4.0 (CTCAE 4.03), uveitis is a very rare side effect occurring in approximately 1% of patients treated with pembrolizumab.[3] Recently, 2 case reports showed that uveitis can lead to grade 3–4 toxicity.[6,7] Uveitis was described several years ago as a frequent adverse effect of adoptive T-cell transfer of in vitro-expanded tumor-infiltrating lymphocytes and is associated with strong immune responses and tumor responses in melanoma patients.[8,9]

PRESENTATION OF 2 CASES

Patient 1

A 60-year-old patient was diagnosed with BRAF wild-type metastatic melanoma in January 2015, without any primary tumor. Imaging studies showed disseminated pulmonary and lymph node metastases (Fig. 1A). First-line treatment with the anti-CTLA4 antibody ipilimumab was started. After 3 cycles without signs of toxicity, a CT scan revealed progressive disease with new liver metastases (Fig. 1B). Treatment was switched to pembrolizumab with

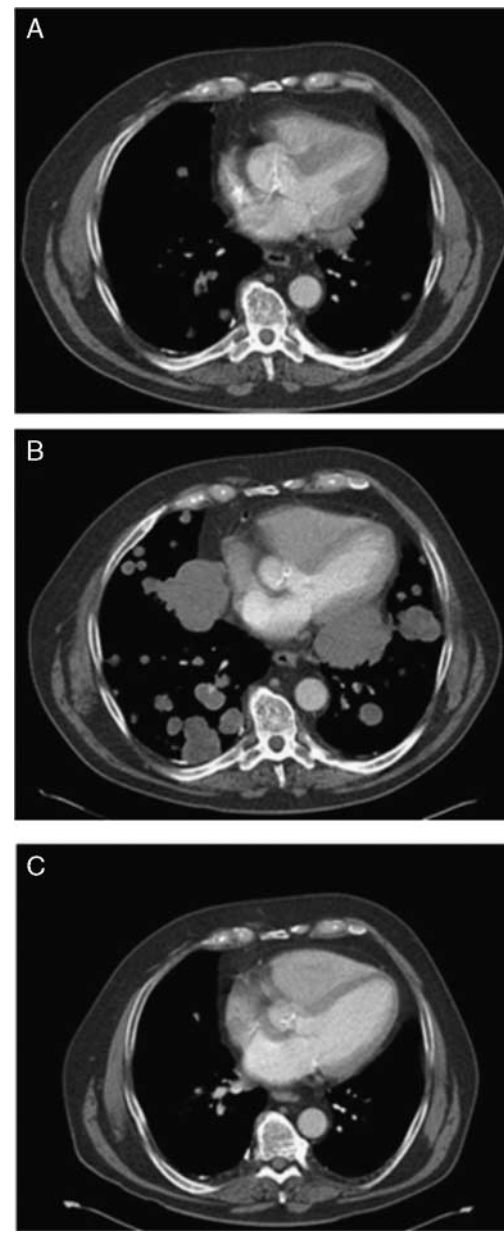

FIGURE 1. Kinetics of lung metastasis before immunotherapy was started (A), after 3 cycles of ipilimumab (B), and at the time point when the patient developed uveitis for the first time (C).

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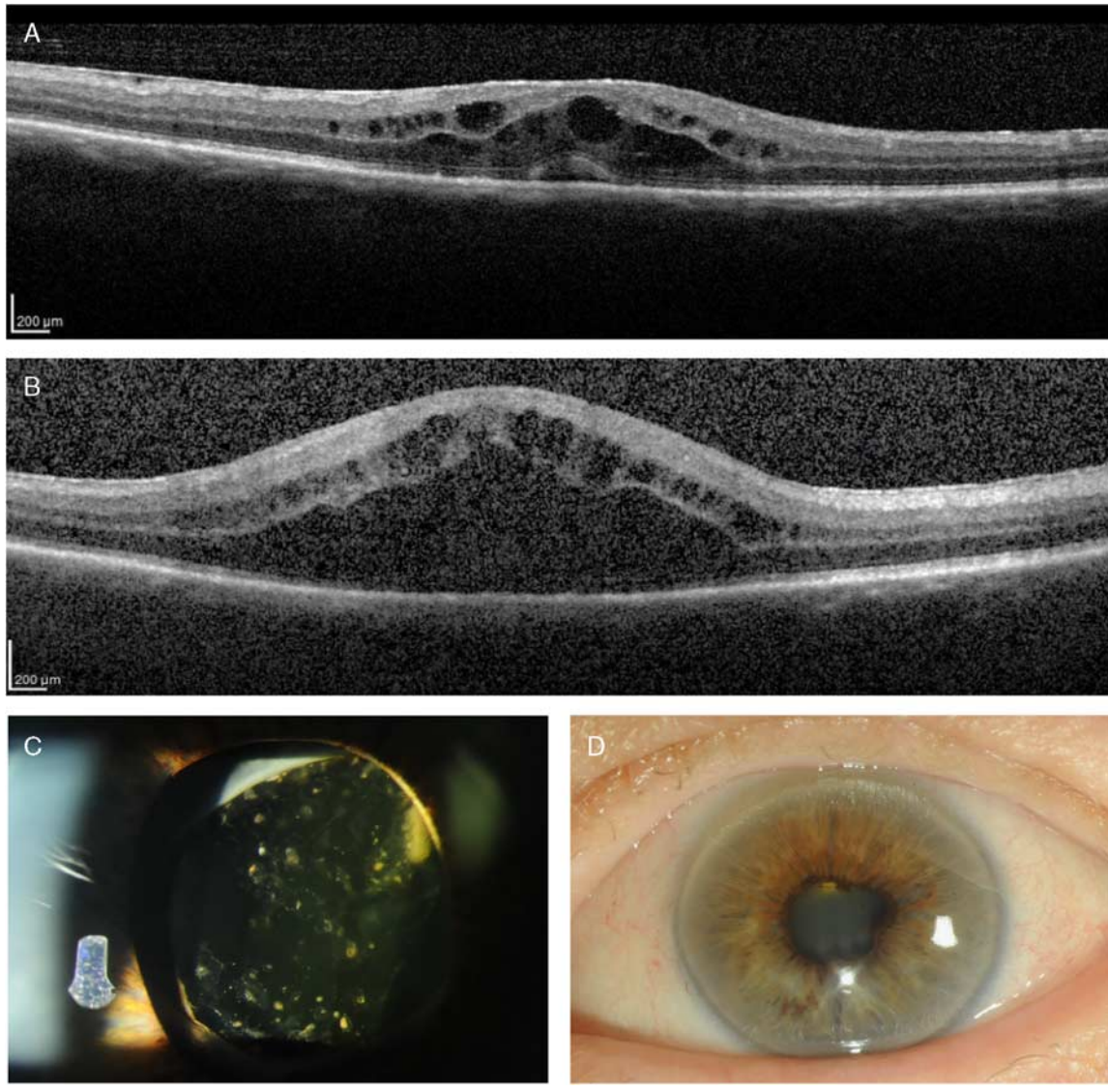

FIGURE 2. Cystoid macular edema after cataract surgery on the right eye. A, Horizontal optical coherence tomography scan centered on the fovea; edema of all retinal layers is present, a subfoveal central serous neuroretinal detachment has developed, and there are large cystic lesions in several inner layers. B, Recurrence of edema after restarting pembrolizumab. Slit-lamp pictures prove signs of bilateral uveitis of the anterior segment 2 months after treatment. C, The right eye with intraocular lens and giant cells. D, The left eye with posterior synechiae and cataract.

the approved standard protocol of 2 mg/kg every 3 weeks. Restaging after 3 months showed a partial tumor remission without any adverse events (Fig. 1C). Pembrolizumab was continued with the same schedule until the patient underwent elective unilateral cataract surgery on the right eye. Within a week, the patient developed bilateral vision problems.

Eye examination showed signs of endophthalmitis with anterior chamber cells in both the right (operated) and left eyes, reduced acuity of vision, and macular edema (Fig. 2A). The patient has had no past medical history of uveitis. Pembrolizumab was stopped and topical treatment with steroids and antibiotics was started. Oral steroids were added and the inflammation regressed, with concurrent improvement of visual acuity. The systemic steroids were tapered without exacerbation. Despite treatment with pembrolizumab having been interrupted, a follow-up CT scan showed an ongoing partial response and pembrolizumab was restarted. Within days, the patient again developed bilateral visual problems and, once again, bilateral posterior uveitis (grade 3 according to CTCAE 4.03) including cystoid macular edemas (Figs. 2B, C).

Systemic steroids were started. Despite immediately stopping pembrolizumab therapy, the most recent CT scan 6 months later showed ongoing partial tumor response.

Patient 2

A 75-year-old man, with stage IV metastatic melanoma, showed progressive disease under ipilimumab and experimental targeted therapy (encorafenib, binimetinib, and LEE011, clinicaltrials.gov NCT01543698) before his treatment was switched to pembrolizumab 2 mg/kg. At the baseline examination before starting the treatment, he presented with bilateral signs of a previously unnoticed uveitis with pupillary adhesions. In the context of this clinical study he underwent regular ophthalmic examinations, including optical coherence tomography (OCT). After 8, 24, and 32

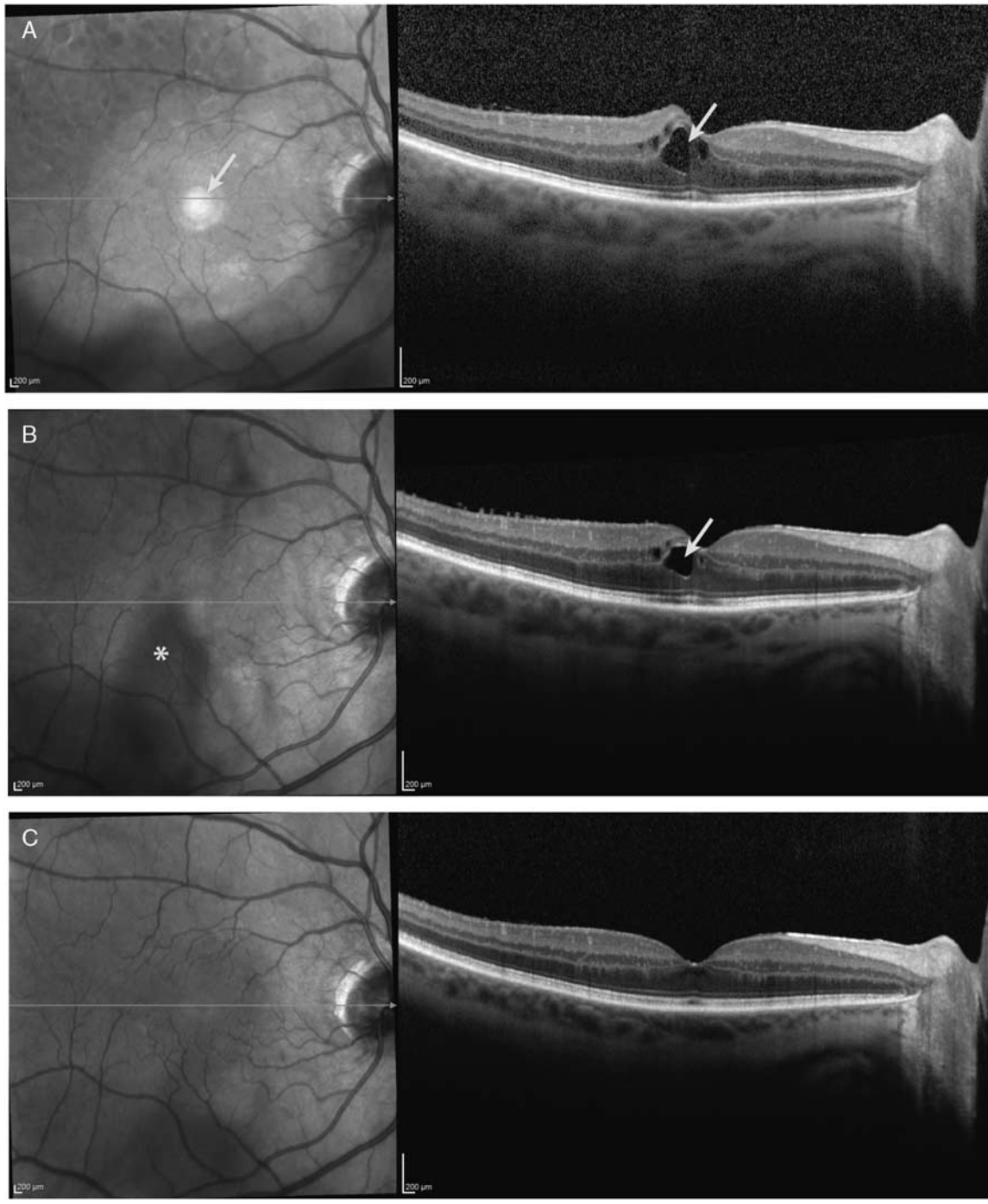

FIGURE 3. Cystoid macular edema during a relapse of bilateral uveitis with posterior-segment involvement after ipilimumab and MEK-inhibitor pretreatment. A, Left: scanning laser ophthalmoscopy (SLO) of the right eye shows a blunted foveal region (arrow) and reduced signals due to vitreous infiltration; Right: horizontal line scan with optical coherence tomography (OCT) confirms 1 large and several smaller cysts (arrow) in the inner retinal layers and deformation of the foveal contour. B, One week later, after intensive topical treatment, the patient had no symptoms and almost normal visual acuity. Right: the SLO image is even more shaded due to increased cellular infiltration (asterisk) of the vitreous; left: OCT scan shows shrinkage of the cyst (arrow). C, Two months later, the inflammation had recovered completely. Right: on SLO the vitreous has cleared; left: the horizontal scan at the same position reveals that the foveal contours have returned to normal and all cysts have disappeared.

weeks, he experienced 3 relapses of bilateral and mostly anterior uveitis with precipitates on the endothelium and iris border, haze, and cellular infiltration. There was only minimal vitreous involvement. Under topical treatment with nepafenac, prednisolone acetate, and scopolamine the inflammation resolved within 2–3 weeks. Following discussion and consideration of this event, the patient consented to a

second course of immunotherapy with pembrolizumab as the potential benefits outweighed the risks. We prescribed prophylactic instillation of nepafenac drops and planned ophthalmic checks after each infusion. As the patient did not experience eye symptoms, he spontaneously discontinued the self-administration of the drops. Three days later, following the fourth infusion in week 8, clinical examination showed mild eye changes with cells in the anterior chamber. We instructed the patient to continue treatment and added prednisolone eye drops. In week 13, he complained of visual disturbances for the first time and ophthalmologic examination showed involvement of the posterior eye segment with cystoid macular edema (Fig. 3A). Intensive topical treatment with steroids, mydriatics, and NSAIDs was started and continued over 2 months. A combination of a β-blocker and a carbonic anhydrase inhibitor, Cosopt (timolol and dorzolamide), had to be prescribed to lower the intraocular pressure. In the course of this intensified topical regimen the patient recovered without functional sequelae (Figs. 3B, C). We were able to continue treatment with pembrolizumab without interruption. During the course of treatment, the patient also developed a skin rash. Skin biopsy revealed a lichenoid reaction pattern, which is commonly seen during anti-PD-1 therapy in melanoma patients. We interpreted the rash as an adverse drug reaction and successfully treated it with topical steroids.

A subsequent PET-CT scan revealed complete regression of the previously described tumor metastasis in the lower lobe of the left lung. Treatment and regular follow-ups are currently ongoing.

DISCUSSION

Uveitis is classified according to the anatomic site of the inflammation in the eye as either anterior, intermediate or posterior uveitis, or panuveitis. The etiology is mostly infective (eg, toxoplasmosis), but can also be autoimmune (eg, HLAB27-associated uveitis). Uveitis is one of the most common reasons for legal blindness.[10] In patients treated with anti-PD-1 antibodies, uveitis is described as a comparatively rare side effect.[3,7] Treatment includes the application of topical steroids and systemic steroids for higher CTCAE 4.03 grades. Most authors describe immunotherapy-associated uveitis to be a toxic effect. In our point of view, immunotherapy-induced uveitis should not only be considered as toxicity but also as the manifestation of an immune response.

On the basis of the literature and our 2 case reports, we would like to outline 3 possible conclusions: firstly, we suggest that patients have ophthalmological examinations, including OCT, before the start of immunotherapy and regular opthalmological follow-up during the treatment. Secondly, similar to vitiligo, uveitis may be considered a surrogate marker for the efficacy of immunotherapy. Sight-threatening cystoid macular edema needs potent treatment, including systemic steroids if needed. Regular OCT examinations in patients at risk help to diagnose this dangerous complication early. However, this adverse event may not initially require high-dose systemic steroids. Rather, we would implement an active surveillance strategy, that is, patients should be monitored closely and given topical NSAIDs prophylactically if they have a history of or are prone to develop uveitis. Steroid drops should be used at the slightest sign of active inflammation. The prophylactic and therapeutic measures should be taken generously over many months.[8,11,12] Finally, the first of our 2 cases demonstrates that care is needed with elective surgery in patients undergoing immunotherapy. Presumably, the cataract surgery triggered bilateral uveitis in this patient. Both PD-1/PD-L1 and CTLA4 axes (checkpoints) are mechanisms to prevent autoimmunity and continued immune destruction (immune pathology) in ongoing disease. The immune privilege of the eye depends partly on the outer blood-retinal barrier of the pigment epithelium. In patients treated with MEK inhibitors, retinopathy with a presumed dysfunction of the pigment epithelium is frequently observed. Therefore, any tissue injury and its biological repair can potentially attract or reactivate immune cells that may subsequently be amplified with checkpoint inhibitors and cause collateral tissue damage.

CONFLICTS OF INTEREST/ FINANCIAL DISCLOSURES

All authors have declared there are no financial conflicts of interest with regard to this work.

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